(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076946 A2

(51) International Patent Classification[7]: C07D 211/00

(21) International Application Number: PCT/EP02/03332

(22) International Filing Date: 25 March 2002 (25.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0107505.0	26 March 2001 (26.03.2001)	GB
60/338,281	6 December 2001 (06.12.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

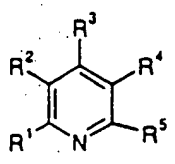
Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/076946 A2

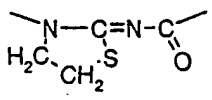
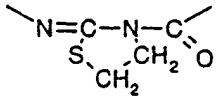
(54) Title: PYRIDINE DERIVATIVES



(I)

(57) **Abstract:** The invention provides compounds of formula I (I) wherein R^1, R^2, R^3, R^4 and R^5 are as defined in the description, and the preparation thereof. The compounds of formula I are useful as pharmaceuticals.

salt form, e.g. as trifluoroacetate or hydrochloride salt. Suitable pharmaceutically acceptable acid addition salts for pharmaceutical use in accordance with the invention include in particular the hydrochloride salt.

More particular examples for R^1 and R^2 include -$NR^{11}C(O)NR^{12}C(O)$-, -NHC(S)NHC(O)-, -NH-C(O)-NH-, -NH-C(S)-NH-, -NH-C(O)-C(O)-NH-, -NH-C(O)-N=C(Cl)-, -NH-C(O)-N=C(OCH_3)-, -NH-C(O)-N=C(NH_2)-, -NH-C(O)-N=CH-, -NH-C(O)-NH-CH_2-, -NH-C(SCH_3)=N-C(O)-, -N=CH-NH-, -N=N-NH-, -N=CH-NH-CH_2-, -N=C[$SCH_2C(O)OC(CH_3)_3$]-NH-C(O)-, -N=CH-NH-C(O)-, -N=C(Cl)-NH-C(O)-, -N=C(NH_2)-NH-C(O)-, -N=C(CH_3)-NH-C(O)-, -N=C(Cl)-N=C(Cl)-, -N=C(Cl)-N=C(NH_2)-, -N=C(OCH_3)-N=C(OCH_3)-, -N=C(OCH_3)-N=C(NH_2)-, -N=CH-N=C(NH_2)-, -N=CH-N=CH-,  and  .

A 5 or 6 membered aromatic or aliphatic heterocyclic ring for R^4 may be e.g. but not limited to thiophenyl, furyl, imidazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperizinyl and derivatives thereof (e.g. C_1-C_4alkyl, OC_1-OC_4alkyl, halogenyl, etc.).

Alkyl groups in the compounds of formula I may be branched or straight chain.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

(a) R^1 and R^2 together are a divalent group -NHC(O)NHC(O)- or -NHC(S)NHC(O)-;

(b) R^3 is hydrogen;

(c) R^4 is phenyl; phenyl substituted by OH, halogen, e.g. chloride, fluoride, C_1-C_6alkyl, C_1-C_6haloalkyl or C_1-C_6alkoxy; and

(d) R^5 is branched or un-branched C_1-C_6alkyl, e.g. isopropyl, tert. butyl or C_3-C_6cycloalkyl.

Most preferred are compounds of formula I wherein R^1 and R^2 together are –NH-C(S)-NH-C(O)-; R^3 is hydrogen; R^4 is phenyl; or phenyl substituted by halogen, C_1-C_4alkyl, C_1-C_4haloalkyl or C_1-C_4alkoxy; and R^5 is C_1-C_4alkyl; or C_3-C_6cycloalkyl.

The invention also provides a process for the production of a compound of formula I comprising the step of

reaction for the first 12-20 hours, the temperature of the reaction solution is kept below 75°C, preferably below 73°C. Then the reaction is heated to about 100°C for 2-4 hours, preferably 3 hours. The solvent is removed using a toluene – heptane mixture. Other solvent mixtures can be of an aromatic hydrocarbon solvent with a lower aliphatic hydrocarbon (C_3-C_8) solvent. Aqueous workup followed by precipitation gives the free base. The salt forms are made by standard procedures known to the skilled artisan, e.g. 6-(4-chlorophenyl)-7-(1,1-dimethylethyl)-2,3-dihydro-2-thioxo-pyrido[2,3-d]pyrimidine-4(1H)-one is purified either as the potassium salt, followed by conversion to the free acid form and recrystallization from ethanol and water or by isolating the crude free acid form followed by the recrystallization from ethanol and water. Compounds of formula I may be further derivatised to arrive at different compounds of formula I.

Compounds of formula II may be prepared e.g. in a first step by Pd-catalyzed arylation of pinacolone with 4-bromochlorobenzene in toluene in the presence of sodium t-butoxide (1.5-3.0 equivalents) to a ketone intermediate. The Pd catalyst is Palladium acetate or other palladium catalysts, such as e.g. $Pd_2(dba)_3$. The sodium t-butoxide serves as a base, and other suitable bases such as lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide can be used. This reaction is conducted in a toluene solution. Other solvents can be THF, xylene. The reaction temperature is at about 80-110°C. The crude product in toluene solution is used directly in the next step after extractive removal of palladium by treatment with an aqueous solution of L-cysteine and sodium thiosulfate and azeotropic removal of water. Other methods which serve to remove the catalyst such as charcoal can also be employed. In a second step, the ketone intermediate is e.g. reacted with *N,N*-dimethylformamide dimethyl acetal to prepare the enamine intermediate, 2-(4-chlorophenyl)-1-(dimethylamino)-4,4-dimethyl-1-penten-3-one. This step takes place preferably in toluene, or another suitable aromatic or aliphatic hydrocarbon solvent, at reflux temperature. Compounds of formula II may be e.g. prepared as illustrated in example 1 and 2.

Starting compounds of formula III are known or may be prepared from corresponding known compounds or may be e.g. prepared as illustrated in example 1 and 2.

The compounds of the invention and their pharmaceutically acceptable acid addition salts (hereinafter: the agents of invention) have pharmacological activity and are useful as

Activity specifically as analgesic agents may be demonstrated in accordance with standard test methods, e.g. as described in the following test.

Test: Anti-hyperalgesic effects in a model of neuropathic pain in the rat

The agents of invention are potent and efficacious anti-hyperalgesic agents following oral administration in the following rat model of neuropathic pain. Peripheral neuropathy is induced by partial ligation of the left sciatic nerve. Mechanical hyperalgesia is assessed from paw withdrawal thresholds measured on the ipsilateral (ligated) and contralateral (non-ligated) hindpaws using standard paw pressure methods. Drug effects are studied 11-15 days post ligation. The mean paw withdrawal threshold ± s.e.m. for the left (ligated) paw is compared to that of the right (non-ligated) paw.

The agents of invention are administered, e.g. orally in 20 % cremophor/water in a volume of 1 ml. The post-drug percentage hyperalgesia values are obtained by comparison to the pre-drug value for the right (non-ligated) paw; this enables a true measure of the reduction in hyperalgesia to be obtained without the added complication of any drug effects on the right paw. Single oral administration of the agents of invention produces a highly effective reversal of mechanical hyperalgesia in the partially denervated rat hind paw. The agents of invention produce a reversal of mechanical hyperalgesia at 0.1-100 mg/kg and show a rapid onset of activity with a long duration of action.

The agents of invention are accordingly useful as vanilloid receptor blockers, e.g. in the treatment of diseases and conditions in which vanilloid receptor activation plays a role or is implicated. Such conditions include in particular pain, e.g. bone and joint pain (osteoarthritis), cancer pain, myofascial pain (muscular injury, fibromyalgia) and perioperative pain (general surgery, gynecologic surgery).

The agents of invention are particularly useful in the treatment or prevention of chronic pain, especially inflammatory, e.g. chronic inflammatory pain, inflammatory diseases for example inflammatory airways disease, e.g. (Chronic Obstructive Pulmonary Disease) COPD, or in asthma, cough, urinary incontinence, migraine, visceral disorders (e.g. inflammatory bowel disease), rhinitis, cystitis, e.g. interstitial cystitis, pancreatitis, uveitis, inflammatory skin disorders and rheumatoid arthritis.

Inflammatory or obstructive airways diseases to which the present invention is applicable further include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and, in particular, byssinosis.

Further inflammatory or obstructive airways diseases and conditions for which the agents of invention may be used include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), and bronchitis. The agents of invention may also be used for the treatment of allergic and vasomotor rhinitis.

In addition to the foregoing the agents of invention are also indicated for use in the therapy of septic shock, e.g. as anti-hypovolaemic and/or anti-hypotensive agents, in the treatment of inflammatory bowel disease cerebral oedema, headache, migraine and inflammatory skin disease such as eczema and psoriasis, and inflammatory disorders of the gut, e.g. irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystitis, e.g. interstitial cystitis, nephritis, uveitis.

The agents of the invention can be administered in vivo either alone or in combination with other pharmaceutical agents effective in the treatment of diseases and conditions in which vanilloid receptor activation plays a role or is implicated including cyclooxygenase-2 (COX-2) inhibitors, such as specific COX-2 inhibitors (e.g. celecoxib and rofecoxib) and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. acetylsalicylic acid, Propionic acid derivatives), tricyclic antidepressants (e.g. Anafranil®, Asendin®, Aventyl®, Elavil®, Endep®, Norfranil®, Norpramin®, Pamelor®, Sinequan®, Surmontil®, Tipramine®, Tofranil®, Vivactil®, Tofranil-PM®), anticonvulsants (e.g. carbamazepine, oxcarbazepine, gabapentin), bradykinin B1 or B2 antagonists and $GABA_B$ agonists (e.g. L-baclofen).

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in

(2) A pharmaceutical composition comprising a compound of formula I in free base or pharmaceutically acceptable acid addition salt form as under (1) as active ingredient together with a pharmaceutically acceptable diluent or carrier therefore;

(2') A compound of formula I in free base or pharmaceutically acceptable acid addition salt form for the treatment or prevention of a disease or condition in which vanilloid receptor plays a role or is implicated comprising a compound of formula I and a carrier.

(3) A method for the treatment of any of particular indication hereinbefore set forth in a subject in need thereof which comprises administering an effective amount of a compound of formula I in free base or pharmaceutically acceptable acid addition salt form as under (1);

(3') A method for treating or preventing a disease or condition in which vanilloid receptor plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula I in free base or pharmaceutically acceptable acid addition salt form.

(4) Use of a compound of formula I in free base or pharmaceutically acceptable acid addition salt form for the manufacture of a medicament for the treatment or prevention of a disease or condition in which activity of vanilloid receptor plays a role or is implicated;

(5) A process for the preparation of a compound of formula I in free base or pharmaceutically acceptable acid addition salt form as under (1);

(6) A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a vanilloid receptor antagonist, e.g. a compound of formula I in free base or pharmaceutically acceptable acid addition salt form and a second drug substance, said second drug substance being for example for use in any of the particular indications hereinbefore set forth;

(7) A combination comprising a therapeutically effective amount of a compound of formula I in free base or pharmaceutically acceptable acid addition salt form and a second drug substance, said second drug substance being for example for use in any of the particular indications hereinbefore set forth.

In the examples the following abbreviations are used: DMF: dimethyl formamide; RT: room temperature; THF: tetrahydrofuran; LCMS: Liquid Chromotagrophy mass spectrometry

Example 1: Preparation of 6-benzyl-7-isopropyl-1.H.-pyrido[2,3-.d.]pyrimidine-2,4-dione

(a) Lithium chloride (27 mmol) and copper (I) chloride (13.46 mmol) are weighed into a flame dried 250 mL round-bottomed flask fitted with low temperature thermometer. Dry THF (50 mL) is added and the mixture stirred at RT for 1h to give a cloudy yellow-green solution. This is cooled to –55ºC and isopropylmagnesium chloride (6.75 mL of a 2 M solution in THF, 13.5 mmol) is added. After 15 min hydrocinnamoyl chloride (13.46 mmol) is added quickly at –60ºC and the mixture allowed to warm slowly to RT overnight. The mixture is quenched with water (100 mL) and 35% ammonium hydroxide (20 mL) is added. The mixture is stirred at RT for 1h and then extracted with diethyl ether (3x50 mL). The combined ether extracts are washed with saturated brine (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 4-methyl-1-phenyl-pentan-3-one.

(b) 4-Methyl-1-phenyl-pentan-3-one (10.2 mmol) and *tert.*-butoxybis-(dimethylamino)-methane (16 mmol) are mixed and heated together at 110ºC for 17h. Excess reagent is removed under reduced pressure to give (E/Z)-2-benzyl-1-dimethylamino-4-methyl-pent-1-en-3-one.

(b) (E/Z)-2-Benzyl-1-dimethylamino-4-methyl-pent-1-en-3-one (8.66mmol) and 4-amino-2,6-dihydroxypyrimidine (10.7mmol) are mixed in ethanol (10 mL) and 10% aqueous acetic acid (90 mL). The mixture is heated at 120ºC under an atmosphere of dry nitrogen for 18h, cooled to RT and the colourless solid formed is recovered by filtration. Recrystallisation from 10% glacial acetic acid in isopropanol gives 6-benzyl-7-isopropyl-1.H.-pyrido[2,3-.d.]pyrimidine-2,4-dione. LCMS: MH+ 296; >97% pure at 214 and 254nm, Retention time = 5.72min.

Example 2: Preparation of 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one

(a) 4-Chlorobenzyl bromide (0.1 mol) and dry diethyl ether (200 mL) are placed in a flame-dried, 2-necked round bottomed flask at RT. The solution is stirred under an inert atmosphere while magnesium turnings (0.1 mol) are added portionwise. Trimethylacetonitrile (0.1 mol) is then added, followed by dry m-xylene (100 mL). The reaction is stirred at RT for 1 h and then the diethyl ether is distilled off (oil bath temp. 130ºC). A further portion of tri-

4-bromochlorobenzene in 850 mL of dry toluene. The mixture is heated to a temperature at 95-100°C using a heating mantle temperature set at about 95-125°C over a period of 40 minutes. A solution of 98.1 g of pinacolone in 300 mL of toluene is added over a period of 45 minutes to 1 hour while maintaining the internal temperature at 95-100°C. The mixture is stirred for an additional 9 hours, then cooled to an internal temperature at 23-25°C over a period of 30 minutes. Six hundred (600) g of 15% ammonium chloride solution is added over a period of 10 minutes while maintaining the internal temperature at 20-27°C. The mixture is stirred, the organic layer separated, and washed with 600 mL of saturated sodium chloride solution. The organic layer is charged into a 5 L, 4-necked, round-bottomed flask equipped with a mechanical stirrer, digital thermometer, addition funnel, heating mantle and a condenser with nitrogen inlet-outlet, and a solution of 150.0 g of L-cysteine in 900 mL of water is added. The mixture is heated to an internal temperature at 84-90°C over a period of 40 minutes to achieve reflux, then stirred for an additional 5 hours. After cooling, the aqueous layer is removed, and the organic layer filtered over a Büchner funnel containing a pad of 20.0 g of Celite. After washing the Celite pad with 200 mL of toluene, and saving the filtrate, to the filtrate is added a solution of 75.0 g of L-cysteine and 2.5 g of sodium thiosulfate pentahydrate in 600 mL of water. The mixture is heated to an internal temperature at 78-82°C. White solids formed gradually. The triphasic mixture is stirred at this temperature for an additional 5 hours, then cooled, and the organic layer is separated. The organic layer is filtered over a pad of 20.0 g of Celite and the pad is washed with 200 mL of toluene. The combined filtrates is washed again with 400 mL of saturated NaCl solution. The organic layer is filtered and concentrated to collect about 800 mL of solvent to afford about 1.0 L of crude 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone in toluene, which is used directly in the next step, theoretical Yield: 137.6 g (Pd 2 ppm).

(b') A 3 L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, reflux condenser, and nitrogen inlet-outlet, is charged with 953 g (1.05 L) of a toluene solution containing 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone and 173 g (200 mL) of toluene; then add by pump 232 g (259 mL) of *N,N*-dimethylformamide dimethyl acetal. The solution is heated to an internal temperature at 97-109°C (reflux) and stirred at this temperature for 5 hours. One hundred (100) mL of solvent is distilled off over a period of 0.5 hours. After distillation is stopped, the mixture is heated to an internal temperature at 107-114°C (reflux). The mixture is stirred at this temperature for an additional 1 hour. Three more distillations follow in a similar procedure. Then the reaction mixture is cooled to an internal temperature at 20-25°C over 1 hour, and stirred at this temperature for 1 hour,

pyrido[2,3-.d.]-pyrimidin-4-one. A 12 L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, reflux condenser, nitrogen inlet-outlet, and addition funnel is charged with the 148 g of crude 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one from the preceding step and 5.18 L of ethyl alcohol, 200 proof. The suspension is heated to an internal temperature at 76-80°C (reflux condition, external temperature 85-100°C) over 1 hour and stirred at this temperature for 2 hours to get a clear solution. The mixture is cooled to 70-75°C over 20 minutes and line-filtered by pressure and saved. The solution is added into a 12 L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, reflux condenser, nitrogen inlet-outlet, and addition funnel, and heated to 76-80°C (reflux condition) over 30 minutes 3.11 L of water is added (ratio of ethanol: water: 1.0:0.6 v/v) over a period of 1.5 hours while maintaining the internal temperature at 76-83°C (reflux condition, external temperature 90-115°C). To this is added 0.09 g of pure 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one seeds in a mixture of 2 mL of water and 2 mL of ethanol at an internal temperature of 70-75°C. The reaction mixture is cooled, (crystals come out at about 65°C) to 20-25°C over 2 hours and stirred at this temperature for 12 hours. The solids are collected by filtration over a polypropylene filter paper in a Büchner funnel with suction; the filter cake is washed with 0.6 L of a mixture of ethyl alcohol and water (1:1 v/v) in two equal portions of 300 mL each. The solid is dried under vacuum (10-20 torr) at 60-65°C with nitrogen bleeding until <0.5% LOD to obtain 96 g of 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one. Theoretical Yield: 224 g, Yield: 43% (over 3 steps). Purity: 98.4% (by HPLC Pd (0.02 ppm), toluene (0%), EtOH (0.01%), H_2O (0.27%).

In the following examples compounds of formula I wherein R^1 and R^2 together are $-NR^{11}-C(O)-NR^{12}-C(O)-$ and R^3 is hydrogen are prepared analogously to the above Examples and exhibit the following characterizing data:

NO.	R^4	R^5	R^{11}	R^{12}	HPLC [retention time in Min]
1.1	phenyl	ethyl	H	H	7.19**
1.2	phenyl	ethyl	methyl	H	8.16**
1.3	CN	tert.-butyl	H	H	7.01**
1.4	4-methylphenyl	tert.-butyl	H	H	6.35***

				(0.4H –partially exchanged, br s)
2.7	4-trifluoromethylphenyl	tert.-butyl	7.24***	[M+H]+ = 346/348
2.8	4-methoxyphenyl	tert.-butyl	6.5***	1.17 (9H, s), 3.81 (3H, s), 6.99 (2H, d, J = 8.7Hz), 7.22 (2H, d, J = 8.7Hz), 7.71 (1H, s), 12.6 (0.2H – partially exchanged, br s), 13.1 (0.2H –partially exchanged, br s)
2.9	4-fluorophenyl	tert.-butyl		1.19 (9H, s), 7.29 (2H, m), 7.40 (2H, m), 7.76 (1H, s); $[M-H]^-$ = 328
2.10	2-chlorophenyl	tert.-butyl	6.90***	
2.11	4-hydroxyphenyl	tert.-butyl	5.25*	
2.12	phenyl	methyl	274-275°C	
2.13	3-chlorophenyl	tert.-butyl	7.07***	[M+H]+ = 380
2.14	4-tert.-butylphenyl	tert.-butyl	8.36***	
2.15	3-methoxyphenyl	tert.-butyl	6.5*	
2.16	4-fluorophenyl	isopropyl		1.17 (6H, d), 3.16 (1H, m), 7.33 (2H, m), 7.45 (2H, m), 7.96 (1H, s); $[M-H]^-$ = 314

* LCMS – Kingsorb 3 micron C18 column, 30 mm x 4.6 mm; gradient elution 10 % MeCN in water (+ 0.1 % TFA) to 100 % MeCN over 10 min

** HPLC-System: Column: Merck LiChrosphere 60 RP (RP C-18), solvents: A: H_2O, 0.1 % TFA, B: CH_3CN, 0.1 % TFA, gradient: 5 to 100 % B in 10 min

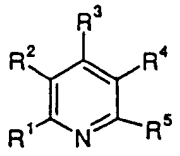
*** Phenomenex C18 R HPLC analytical column, 30 mm x 4.6 mm, gradient: 90:10 to 0:100 (water + 0.1 % TFA:MeCN) over 10 min

In the following examples compounds of formula I are prepared as described above by a variety of transformations and exhibit the following characterizing data:

No.	R^1 and R^2 together	R^3	R^4	R^5	MS data	Melting data [°]
3.1	-N=C(Cl)-N=C(Cl)-	H	phenyl	tert.-butyl	EI-MS: $[M-H]^+$ = 330, 332	135-136
3.2	-NH-C(O)-N=C(Cl)-	H	phenyl	tert.-butyl	EI-MS: $[M-H]^+$ = 312	176-179
3.3	-NH-C(O)-N=C(OCH_3)-	H	phenyl	tert.-butyl	ES-MS: $[M-H]^-$ = 308	254-256 (hydrochloride)
3.4	-NH-C(SCH_3)=N-C(O)-	H	phenyl	tert.-butyl	ES-MS: $[M-H]^-$ = 324	> 250
3.5	-N=C(Cl)-NH-C(O)-	H	phenyl	tert.-butyl	ES-MS: $[M-H]^-$ = 312; ES+MS: $[MH]^+$ = 314	

Claims

1. A compound of formula I



(I)

wherein

R^1 and R^2 together are -NH-C(SR^6)=N-C(O)-, -NR^7-C(R^8)=N-C(O)-, -N=C(SR^9)-NR^{10}-C(O)-, -NR^{11}-X-NR^{12}C(O)-, -NH-X-NH-, -NH-X-N=C(R^{13})-, -NH-X-NH-CH_2-, -N=Z-NH-, -N=Z-NH-CH_2-, -N=Z-NH-C(O)- and -N=Z-N=C(R^{14})-, wherein X is C(O), C(S) or C(O)-C(O); Z is N or CR^{15}, R^6 is C_1-C_4alkyl; R^7 and R^8 are each independently hydrogen, C_1-C_4alkyl, C_3-C_8cycloalkyl or form together with the adjacent atoms a 5 or 6 membered heterocyclic ring; R^9 and R^{10} together are C_1-C_4alkyl; R^{11} is hydrogen; C_1-C_4alkyl; C_1-C_4alkyl substituted by C(O)OC_1-C_4alkyl; or phenyl substituted by C_1-C_4alkyl; R^{12} is hydrogen, NH_2; C_1-C_4alkyl; or phenyl substituted by C_1-C_4alkyl; R^{13} is hydrogen, halogen, NH_2 or C_1-C_4alkoxy; R^{14} is hydrogen, hydroxy, halogen, NH_2, C_1-C_4alkyl or C_1-C_4alkoxy; and R^{15} is hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy or $SCH_2C(O)OC(CH_3)_3$;

R^3 is hydrogen; OH; CN; C_1-C_6alkyl; phenyl; or C(O)OC_1-C_4alkyl;

R^4 is hydrogen; halogen; NH_2; CN; C_1-C_6alkyl; C_1-C_6alkyl substituted by OH; phenyl; phenyl substituted by OH, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl or C_1-C_6alkoxy; benzyl; benzoyl substituted by OH; or C(O)OC_1-C_6alkyl; 5 or 6 membered aromatic or aliphatic heterocyclic ring;

R^5 is hydrogen; OH; NH_2; halogen; C_1-C_6alkyl; C_1-C_6alkyl substituted by halobenzyl; C_3-C_6cycloalkyl; phenyl; pyridinyl; NHC_1-C_4alkyl; or N=CHN(C_1-C_4alkyl)$_2$;

with the proviso that compounds of formula I are not pyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione and 6-chloro-2-methyl-4-oxo-pyrido[3,2-d]pyrimidine;

in free base or acid addition salt form.

2. A compound of formula I which is 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one in free base or acid addition salt form.

3. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, comprising the step of

9. A method for treating or preventing a disease or condition in which vanilloid receptor activation plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

10. The process of making 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one or a salt thereof, comprising the steps of:
i) preparing the compound 1-(4-chlorophenyl)-3,3-dimethyl-2-butanone by Pd-catalyzed arylation of pinacolone with 4-bromochlorobenzene in toluene in the presence of sodium t-butoxide; followed by treatment of the resulting intermediate with an aqueous solution of L-cysteine and sodium thiosulfate and azeotropic removal of water to produce the intermediate 2-(4-chlorophenyl)-1-(dimethylamino)-4,4-dimethyl-1-penten-3-one; which is then treated
ii) with *N,N*-dimethylformamide dimethyl acetal and then

iii) reacting the intermediate 2-(4-chlorophenyl)-1-(dimethylamino)-4,4-dimethyl-1-penten-3-one with 4-amino-6-hydroxy-2-mercaptopyrimidine monohydrate in toluene and acetic acid at 70°C for 15 hours, then at 100°C for 2 hours;
and purifying and recovering the obtained compound, in free base or in acid addition salt form.

11. The process of making 7-.tert.-butyl-6-(4-chlorophenyl)-2-thioxo-2,3-dihydro-1.H.-pyrido[2,3-.d.]-pyrimidin-4-one or a salt thereof, by reacting the intermediate 2-(4-chlorophenyl)-1-(dimethylamino)-4,4-dimethyl-1-penten-3-one with 4-amino-6-hydroxy-2-mercaptopyrimidine monohydrate in toluene and acetic acid at 70°C for 15 hours, then at 100°C for 2 hours, and purifying and isolating the desired final product.

12. A combination which comprises (a) a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid salt form and (b) a second drug substance, said second drug substance being for example for use in the treatment and prevention of chronic pain, osteo and rheumatoid arthritis, teno-synovitis and gout, wherein the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.